Rare Subtype of Medication-Related Osteonecrosis of the Jaw: Imaging Findings and Treatment Outcomes of Periosteal Reaction Dominant Type

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Abstract

Purpose

In our previous study, we found a rare type of medication-related osteonecrosis of the jaw (MRONJ), which shows periosteal reaction (PR) at a site distant from the osteolytic lesions or extraction site (periosteal reaction dominant type: PRd type), even though the osteolytic lesions in the bone marrow are localized. Given that the causes and treatment of MRONJ remain unclear, this study aimed to describe the imaging and clinical features of the PRd type.

Methods

Patients with MRONJ who visited Nagasaki University Hospital during 2009-2020 and received conservative therapy as the initial treatment were included in this study. Site of PR, imaging findings, initial symptoms, outcome, and time to progression were examined.

Results

Of the 59 MRONJ patients treated with conservative therapy, 38 did not show PR (PR- type), 15 showed PR near the osteolytic region (PR+ type), and six had the PRd type. All patients with the PRd type had submental abscesses, and computed tomography (CT) images demonstrated PR on the lingual side of the anterior mandible. Osteolytic lesions progressed in 6/6 PRd type (100%), 5/15 PR+ type (33.3%), and 2/38 PR- type (5.3%) patients. Time to progression for the osteolytic region on CT was short for the PRd type, at 56-148 days (median, 79 days).

Conclusion

Among the MRONJ types, the PRd type has a poor prognosis. Therefore, it is necessary to accumulate and analyze more PRd cases in the future. This is the first report to report the presence of this specific subtype of MRONJ,

Introduction

Bone-modifying agents (BMA) such as bisphosphonates (BP) and denosumab (Dmab) are widely used as first-line agents for the prevention of osteoporosis-related fractures and the treatment of skeletal-related events in malignant tumors or multiple myeloma [1]. Although these drugs have a strong inhibitory effect on bone resorption, the development of medication-related osteonecrosis of the jaw (MRONJ), as a serious late adverse event, is a major problem. Moreover, the causes and treatment of MRONJ remain unclear thus far. Conservative treatment has been recommended as the first-line treatment, but surgical treatment is also an option when conservative treatment fails to show good results [2]. In our previous study, we found that surgical treatment was significantly better than conservative treatment for MRONJ in a multicenter retrospective study [3].

Computed tomography (CT) images may show a periosteal reaction (PR) in MRONJ. It has been reported that MRONJ with PR often has poor outcomes, even after surgical treatment [4]. It has also been reported that PR in MRONJ can be classified into three types based on the CT images: type 1, when a new bone is formed parallel

to the mandible and no gap is evident between the mandible and the new bone; type 2, when a new bone is formed parallel to the mandible and a gap is evident between them; and type 3, with an irregular shape [5]. Among them, patients with type 3 PR showed poor treatment outcomes and the PR region should be included in the resection area. Although PR in MRONJ is one of the most important factors when considering the treatment and prognosis, its true nature and causes remain largely unknown. PR is thought to be formed by the extension of the lesion in the bone marrow and perforation of the cortical bone, but in rare cases, we have seen extensive PR spread to areas distant from the osteolytic lesions, even though the lesions in the bone marrow were localized. We named it the PR dominant type (PRd type). The purpose of this study was to describe the imaging findings and clinical features of the PRd type.

Materials And Methods

Patients

Fifty-nine patients with MRONJ who visited Nagasaki University Hospital between 2009 and 2020, and underwent conservative therapy as the initial treatment, including antibiotic mouthwash and antibiotics, were included in the study. CT images taken at the time of the initial examination were classified into three types: 1) PRd type: if PR was located away from the osteolytic lesion or extraction site, 2) PR + type: if PR was coincident with the osteolytic lesion or extraction site, and 3) PR- type: if PR was absent.

Methods

For each subtype, we recorded data of patients' age, sex, site of MRONJ (upper/lower jaw), primary disease (osteoporosis/malignant tumor), type of BMA (BP/Dmab), administration period of BMA, corticosteroid use, presence of diabetes, stage, site of PR, initial symptoms, outcome (progression/no change/improvement), time period from initial diagnosis to disease progression (number of days until CT images or pantomography images showed progression of the osteolytic lesion compared to the initial diagnosis), white blood cell count, serum albumin, and serum creatinine. Interpretation of CT images and panoramic radiography was performed by a radiologist (MSu, YT, or MSa) and an oral surgeon (MU, SY, or SH), blinded to the clinical course. All statistical analyses were performed using SPSS software (version 24.0; Japan IBM Co., Ltd., Tokyo, Japan). The association of each variable with MRONJ was analyzed using the Mann-Whitney U nonparametric test for ordinal variables and Fisher's exact test for categorical variables. Probabilities of less than 0.05 were accepted as significant.

Results

Characteristics of the PRd type

We observed six cases of the PRd type in 59 MRONJ patients treated with conservative therapy. Data of the demographic factors and clinical features of all PRd-type patients are summarized in Table 1. The age of the patients ranged from 86 to 90 years, with a median age of 87 years. The primary disease was a malignant tumor in two patients and osteoporosis in four. All six patients developed MRONJ in the lower jaw.

Comparison of clinical features between the PRd, PR+, and PR- types

Of the 59 patients, 15 had the PR+ type, 38 had the PR- type, and six had the PRd type. A comparison of the demographic and clinical features between the three types is presented in Table 2. The PRd type tended to be more common in the elderly ($p<0.001$). Additionally, the PRd type showed more PR on the lingual side of the mandibular body than the PR+ type ($p<0.001$). The initial symptoms in patients with the PRd type manifested outside the oral cavity in the form of a submental abscess significantly more often than those in the PR+ type ($p=0.001$) and the PR- type ($p<0.001$). The oral cavity in patients with the PRd type was asymptomatic, or only mildly infected and painful. There were no differences in the sex, primary disease, type of BMA, duration of administration of BMA, corticosteroid use, presence of diabetes, leukocyte count, serum albumin level, and serum creatinine level.

Imaging findings of the PRd type

CT images of the PR+ type showed PR consistent with an osteolytic lesion (Fig. 1).

The PRd type demonstrated diffuse sclerosis in the mandibular body away from the osteolytic lesion on CT images, and irregular PR was seen extending from the lingual side of the mandibular body to the inferior margin of the mandible (Fig. 2). As the MRONJ progresses, the cortical bone exhibits changes that are consistent with PR resorption from the outside, with subsequent ossification. In addition, sclerosis and osteolytic lesions develop in the bone marrow (Fig. 3).

Treatment outcome of PRd type

Regarding the treatment outcome, the clinical symptoms of all six patients with the PRd type showed exacerbation. However, disease progression was seen in 5/15 (33.3%) PR+ type patients and 2/38 (5.3%) PR- type patients. There was a statistically significant difference between the treatment outcomes of the PRd type and PR+ type ($p=0.022$), and between the PRd type and PR- type ($p<0.001$) (Table 3). The mean period until the progression of the osteolytic lesions was as short as 79 days in patients with the PRd type, in contrast to 241 days for the PR+ type and 239 days for the PR- type (Table 3).

Discussion

It was previously reported that PR was sometimes observed in MRONJ [6]; however, its clinical significance has not been clarified. Kojima et al. reported that post-surgical outcomes were significantly worse in patients with PR [4]. Soutome et al. classified PR into three types according to the CT images and found bacterial infection in the radiolucent area of PR by histological examination and real-time polymerase chain reaction (PCR) [5]. Regarding the extent of osteotomy, they stated that complete healing could not be achieved if irregularly shaped PR persisted after surgery.

While conducting research on PR in MRONJ, we noticed a rare type of PR, which we named the PRd type. Soutome et al.[5] described the possible mechanisms of PR as follows: When bacterial infection in the bone marrow extends to the cortex, type 1 PR (attached type) occurs initially as a protective response. Next, if the infection overwhelms the host immunity, a gap consisting of an abscess and inflammatory granulation tissue is formed between the mandible and PR site, resulting in type 2 PR (gap type). Furthermore, if the infection is aggressive and extends to the periosteum faster than the rate of bone formation under the periosteum,

perforation of the periosteum and an irregularly shaped PR may occur, resulting in type 3 PR (irregular type). However, the PRd type reported in the present study showed almost no bone resorption in the mandibular body near the PR and may be considered a rare variant to which the hypothesis of Soutome et al. [5] does not apply.

We propose two hypotheses regarding the mechanism of development of the PRd type. The first hypothesis (progress through the bone marrow) is that the MRONJ infection in the bone marrow rapidly progresses through the bone marrow cavity at a faster rate than the bone resorption occurs, and these lesions perforate the lingual cortical bone and result in an extended PR. There was no inferior alveolar artery in the anterior mandible between the bilateral mental foramen, and the blood circulation was originally low. In addition, administration of an antiresorptive agent further impairs the blood circulation and reduces the ability to protect against infection. Therefore, infection in the medullary cavity of the anterior mandible may spread rapidly. The second hypothesis (progress vis periosteum) is that the MRONJ infection perforating the lingual cortical bone spreads rapidly along the periosteum on the lingual side of the mandible. In the PRd type, inflammation of the soft tissues surrounding the PR is observed on magnetic resonance (MR) images, which can damage the periosteum, resulting in physical disruption of blood flow from the periosteum and, consequently, extensive bone ischemia. Bacterial infections of the soft tissues can also directly cause osteolytic lesions. Both mechanisms can cause widespread bone destruction, which is consistent with the clinical progression. The PR of the PRd type is located on the lingual side of the mandibular body up to the inferior border of the mandible, and the initial sign is a submental abscess. The reason for this is that suprahyoid muscles such as the mylohyoid muscles are attached to the lingual side of the mandibular body and physically pull the periosteum backward, which may lead to the progression of ischemia. In addition, impaired blood flow from the lingual foramen due to PR, invasion of bacteria into the bone marrow, and low bone marrow volume in the mandibular anterior region may also be considered as contributing factors. Even if the PRd type is diagnosed at an early stage, it is difficult to choose segmental resection due to only a slight osteolytic lesion. In the future, it will be necessary to accumulate PRd type cases and establish an appropriate surgical method.

This study has some limitations. First, because this was a single-center and small-scale study, it is unclear whether the results can be generalized. Second, no histological or bacteriological investigations were performed on the patients with the PRd type; therefore, its etiology has not been identified. However, to the best of our knowledge, this is the first report to clarify the existence of this specific subtype of MRONJ, and it has considerable clinical significance. In the future, we would like to collect additional PRd-type cases and investigate their pathophysiology and appropriate treatment methods.

Conclusions

Our study demonstrated that there is a rare variant of MRONJ, which shows extended PR at a site distant from the osteolytic lesions or the extraction site, despite the presence of few osteolytic lesions. This type (PRd type) progresses rapidly despite conservative therapy and has poor treatment outcomes. It is necessary to examine a large number of cases and establish treatment methods in the future.

Declarations

Funding

N/A

Conflicts of interest/Competing interests

N/A

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

N/A

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Saki Hayashida, Souichi Yanamoto, Miho Sasaki, Yukinori Takagi, Misa Sumi, Masahiro Umeda. The first draft of the manuscript was written by Mitsunobu Otsuru and Sakiko Soutome and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the Institutional Review Board (#21021509) of Nagasaki University Hospital.

Consent to participate

Because this was a retrospective study, the research plan was published on homepage of the participating hospitals according to the instructions of the IRB in accordance with the guaranteed opt-out opportunity.

Consent for publication

N/A

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Tables

Table 1 Patients of PRd type

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	male	male	female	female	female	female
Age	87	88	87	90	86	86
Primary disease	malignant tumor	malignant tumor	osteoporosis	osteoporosis	osteoporosis	osteoporosis
Sort of BMA	BP	BP/Dmab	Dmab	BP/Dmab	BP	BP
Administration period of BMA(months)	31	78	10	60	unknown	unknown
Site of MRONJ	lower jaw	lower jaw	lower jaw	lower jaw	lower jaw	lower jaw

Table2 Demographic characteristics of 59 patients.

Factors		PRd type	PR+ type	PR- type	p^a	p^b
Sex	male	2	6	10	1.000	0.658
	female	4	9	28		
Age (years)	<85	0	1	28	<0.001	0.001
	≥ 85	6	14	10		
Site	upper jaw	0	2	12	1.000	0.167
	lower jaw	6	13	26		
Site of PR	lingual side of the front teeth	6	1	0	<0.001	0
	buccal side of the front teeth	0	0	0		
	lingual side of the molar teeth	0	5	0		
	buccal side of the molar teeth	0	7	0		
	upper jaw	0	2	0		
Primary disease	osteoporosis	4	4	18	0.146	0.664
	malignant tumor	2	11	20		
Type of BMA	BP	3	10	25	0.286	0.083
	Dmab	1	4	11		
	both	2	1	2		
Administration period of BMA	<4 years	2	5	17	0.054	0.318
	≥ 4 years	2	10	17		
	unknown	2	0	4		
Corticosteroid	-	5	14	27	0.500	1.000
	+	1	1	11		
Diabetes	-	6	11	32	0.281	0.391
	+	0	4	6		
Initial symptom	intra-oral	0	12	37	0.001	<0.001
	extra-oral	3	0	1		
	both	3	3	0		
Leukocytes count (/ μ L)	range (median)	4700-8500	3600-7600	3100-18100	0.779	0.307

		(6400)	(6500)	(7700)		
Serum albumin (g/dL)	range (median)	2.6-4.0 (3.7)	3.0-5.0 (4.1)	2.6-4.7 (3.5)	0.130	0.556
Serum creatinine (mg/dL)	range (median)	0.65-2.35 (0.87)	0.60-1.87 (0.84)	0.43-3.09 (0.79)	1.000	0.717
MRONJ stage	stage 1	0	1	5	0.004	0.001
	stage 2	0	11	25		
	stage 3	6	3	8		

P^a: PRd type versus PR+

P^b: PRd type versus PR-:

Table 3 Comparison of treatment outcome between PR-d, PR+, and PR- types

		PRd type	PR+ type	PR- type	<i>p</i> ^a	<i>p</i> ^b
Treatment outcome	improvement	0	1	13	0.022	<0.001
	no change	0	9	23		
	progression	6	5	2		
Duration until progression (days)	range (median)	56-148 (79)	104-466 (241)	227-251 (239)	0.017	0.071

P^a: PRd type versus PR+

P^b: PRd type versus PR-:

Figures

Figure 1

PR+ Type: Periosteal reaction (PR) was observed (arrow) consistent with the osteolytic lesion

Figure 2

PRd Type: The patient was an 88-year-old man. On initial examination, computed tomography (CT) images showed diffuse sclerosis in the mandibular body at a distance from the osteolytic lesion, along with irregular periosteal reaction (PR) extending from the lingual side of the mandibular body to the inferior border of the mandible. (A: curved multi-planar reconstruction; B: axial; C: coronal; D: median sagittal).

Figure 3

PRd Type: As medication-related osteonecrosis of the jaw (MRONJ) progresses, cortical bone consistent with the periosteal reaction (PR) resorbs from the outside and then sequesters. In the bone marrow, sclerosis and osteolytic lesions develop. (A: curved multi-planar reconstruction; B: axial; C: coronal; D: median sagittal).